

Use of scatter correction in quantitative I-123 MIBG Scintigraphy for differentiating patients with Parkinsonism: Results from Phantom experiment and Clinical Study

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Abstract

The aims of this study were to elucidate the feasibility of scatter correction in improving the quantitative accuracy of the Heart-to-Mediastinum (H/M) ratio in I-123 MIBG imaging and to clarify whether the H/M ratio calculated from the scatter corrected image improves the accuracy of differentiating patients with Parkinsonism from other neurological disorders. The H/M ratio was calculated using the counts from planar images processed with and without scatter correction in the phantom and on patients. The triple energy window (TEW) method was used for scatter correction. Fifty five patients were enrolled in the clinical study. The Receiver Operating Characteristic (ROC) Curve analysis was used to evaluate diagnostic performance. The H/M ratio was found to be increased after scatter correction in the phantom simulating normal cardiac uptake, while no changes were observed in the phantom simulating no uptake. It was observed that scatter correction stabilized the H/M ratio by eliminating the influence of scatter photons originating from the liver, especially in the condition of no cardiac uptake. Similarly, scatter correction increased the H/M ratio in conditions other than Parkinson's disease but did not show any change in Parkinson's disease itself to widen the differences in the H/M ratios between the two groups. The overall power of the test did not show any significant improvement after scatter correction in differentiating patients with Parkinsonism. Based on the results of this study it has been concluded that scatter correction improves the quantitative

accuracy of H/M ratio in MIBG imaging, but it does not offer any significant incremental diagnostic value over conventional imaging (without scatter correction). Nevertheless it is felt that the scatter correction technique deserves special consideration in order to make the test more robust and obtain stable H/M ratios.

Key words: MIBG Imaging, Parkinson's disease, Parkinsonism, Scatter Correction, Triple Energy Window.

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Introduction

Iodine 123 labeled Metaiodobenzylguanidine (I-123 MIBG), a norepinephrine analogue which is taken up and stored in the sympathetic nerve endings has been used to evaluate cardiac sympathetic nerve function (1). A number of investigators have reported the reduction in cardiac MIBG uptake in patients with Parkinson's disease (PD) and Dementia with Lewy Body (DLB) and its relative preservation in other neurological disorders like multiple system atrophy (MSA) and Cerebrovascular disease (CVD) (2-7). The authors of all the above cited reports have used quantitative methods to determine MIBG uptake in the determination of cardiac sympathetic nerve function. The index which has been most frequently used by most investigators is the heart to mediastinum (H/M) ratio that denotes the ratio of MIBG uptake in the myocardium over that in the mediastinum in an anterior planar image. The H/M ratio has proven to be very useful and shown relatively lower intra-subject variation (1). However, Nagayama and co-authors in a recently published study have reported considerable overlap in the values of H/M ratio between PD and non-PD patients (8), suggesting thereby the limitation of this parameter in differentiating patients with Parkinsonism from other neurological disorders. There are at least two conceivable reasons which could account for this overlap: 1. The real overlap of cardiac MIBG uptake values between the groups and 2. Technical error in calculating H/M ratios.

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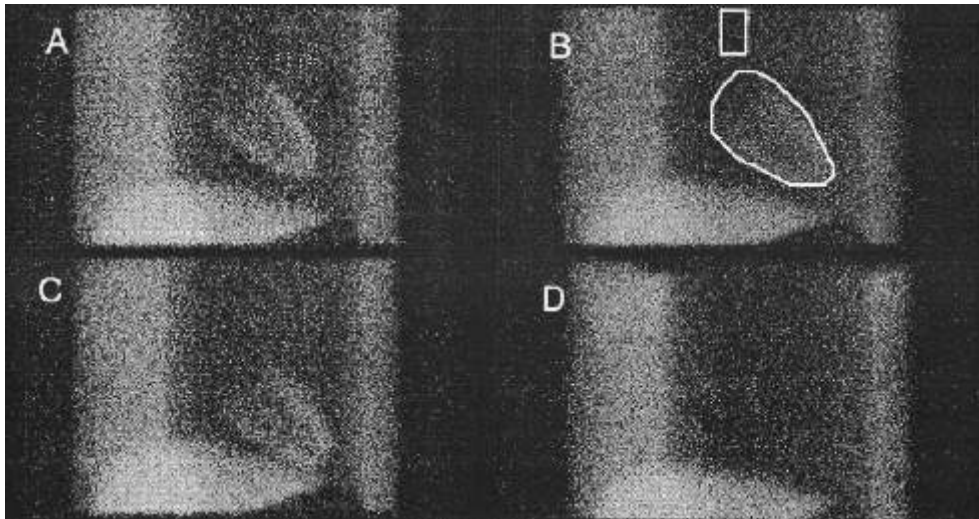


Figure 1. Configuration of the thoracic phantom. Panels A,B and C show the images obtained from the phantom containing the cardiac insert positioned far, normal (in between far and near) and near from liver, respectively. Panel D demonstrates the condition of no cardiac uptake. ROIs for heart and mediastinum are superimposed on the image of Panel B.

With regard to the technical aspects in the measurement, the problem caused by scattered photons in the region of interests (ROIs) is not negligible. This has been reported by several investigators (9-11). These reports have shown that reduction in the number of scattered photons by employing appropriate collimation and/or methods of scatter correction has improved the accuracy of H/M ratio in phantom experiments. In addition, clinically in patients suffering from cardiac diseases, scatter correction has been reported to increase the value of H/M ratio and decrease the variations caused by different collimations used (9). On the other hand, patients with PD often manifest no cardiac uptake of MIBG (3,5), and the effect of scatter reduction in images of such patients remains unclear. Nevertheless, there are few reports which have addressed the effect of correction in differentiating patients with Parkinsonism from other neurological disorders.

The aims of the present study were to elucidate the usefulness of scatter correction in the accurate quantification of the H/M ratio under different conditions of MIBG uptake and to clarify whether the H/M ratio obtained from scatter corrected images improves the accuracy of differentiating patients with Parkinsonism. We performed phantom experiments simulating patients with variable degrees of severity of nerve dysfunction and enrolled PD and non-PD patients in the clinical study.

Materials and Methods

A thoracic phantom (Kyoto-kagaku, Co., Kyoto, Japan) with a cardiac insert and the structures of mediastinum, lung, liver, stomach and vertebrae was used in this study (Figure 1). The cardiac insert consists of the left ventricular wall (120 ml), the left ventricular cavity (95 ml) and right ventricular cavity (105 ml). The compartmental volumes of

the phantom were 2850 ml for the mediastinum including the cardiac insert, 710 ml for right lung, 540 ml for left lung, 1100 ml for liver and 290 ml for stomach. The distance between the cardiac insert and liver is adjustable.

Different radioactivity concentrations of I-123 MIBG (Daiichi Radioisotope Laboratories Ltd., Tokyo, Japan) were prepared for the left ventricular wall, liver, lung and mediastinum. The condition of normal cardiac nerve function was simulated by filling the left ventricular wall with 44.4 kBq/ml (1.2 μ Ci/ml) of I-123 MIBG, and the condition of no cardiac was simulated by removing the cardiac insert. Other concentrations were 29.6 kBq/ml (0.8 μ Ci/ml) for the liver, 23.7 kBq/ml (0.64 μ Ci/ml) for the lungs and 3.0 kBq/ml (0.08 μ Ci/ml) for the mediastinum. Thus the proportions of radioactive concentration in the heart, liver, lung and mediastinum were approximately 15:10:8:1 and 0:10:8:1 respectively corresponding to the conditions of simulated normal function and no cardiac uptake. The left and right ventricles and the stomach cavities were filled with water without radioactivity. Therefore the mean count per pixel in the liver ROI is higher than that in the cardiac ROI covering the whole heart, although radioactive concentration in the heart is 1.5 folds higher than that in the liver. On the setting of normal nerve function the position of the cardiac insert was changed to simulate the variations in the proximity of heart to the liver; e.g., very near, normal and away from the liver (Figure 1).

Clinical Study

Fifty-five patients, aged 63.0 ± 14.7 years were included in the present study during the period from June 2004 to September 2005. The diagnosis of the clinical conditions is given in Table-1. The patients were divided into two categories: PD and non-PD categories. PD patients were diagnosed using the United Kingdom Parkinson's Disease

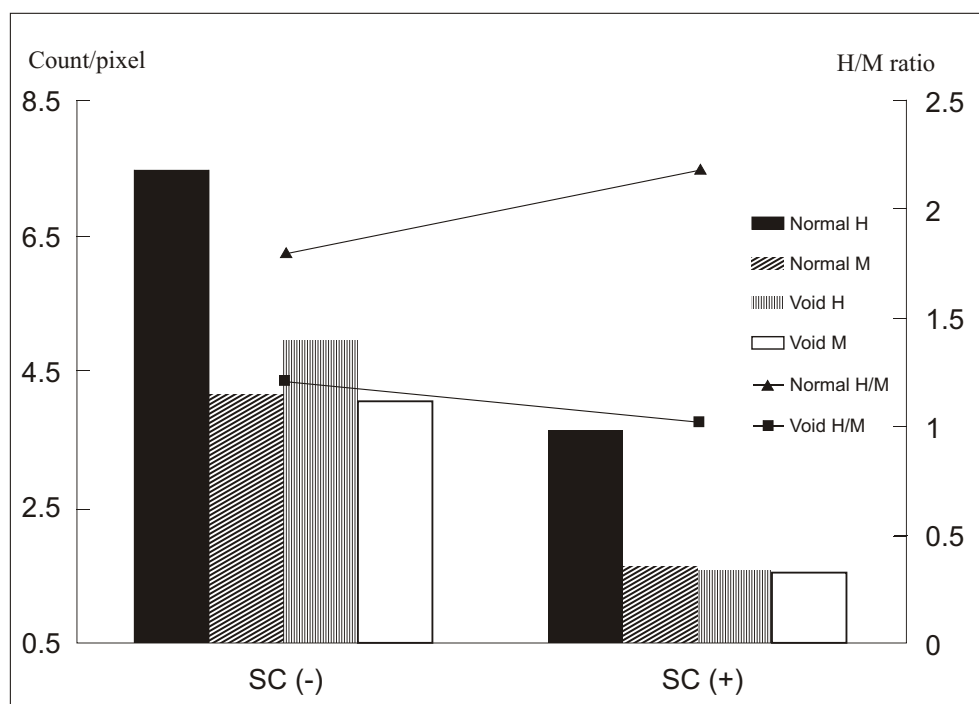


Figure 2. ROI counts and H/M ratios obtained with and without scatter correction. Bars represent the counts per pixel and the lines indicate the H/M ratios. Normal: Normal cardiac uptake; Void: No cardiac uptake; H: Heart; M: Mediastinum; H/M: heart-to-mediastinum count ratio; SC(-): without scatter correction; SC(+): With scatter correction.

Society Brain Bank Clinical Diagnosis Criteria (12,13). Individuals with the history of cardiac diseases or other factors possibly affecting sympathetic nerve function such as diabetes mellitus and antipsychotic drug administration were excluded. Informed consents were obtained from each patient before the examination. This study was conducted according to the Governmental and Institutional Regulations for protection of data privacy and confidentiality.

Data acquisition

Both in phantom as well as clinical studies, anterior planar images were obtained using a gamma camera system (GCA-9300A, Toshiba Corporation, Tokyo, Japan) equipped with a low energy, high resolution and parallel-hole collimator. According to the triple energy window (TEW) method (14,15), the acquisition windows used were as follows: 20% energy main window centered on the 159 keV photo-peak and two 7% sub-windows on both sides of the main window. Counts were acquired for 300 seconds on a 512x512 matrix. In the clinical study, images were acquired 3 hours after intravenous injection of 111 MBq (3 mCi) of I-123 MIBG.

Image Processing and Data Analysis

The data were processed with a medical image processor (GMS-5500A, Toshiba Corporation, Tokyo, Japan). Planar images with and without scatter correction were used for data analysis. In the TEW scatter correction method, the scatter fraction in the main window was estimated by the trapezoidal approximation based on first obtaining the counts in the sub-windows and then subtracting the same

from the count in the main window to obtain a scatter-corrected image as in the previous studies (14,15). The order and cut-off frequency of the pre-filter for the sub-window were 8 and 0.07 (cycles/pixel), respectively. Filtering was not performed on the data of the main window. The selection of the filtering parameters was based on the results of our preparatory study performed prior to the present study (unpublished data). The image without scatter correction was generated only from the data in the main window.

A cardiac ROI was drawn manually over the contour of the heart and a rectangular mediastinal ROI was drawn in the upper mediastinum (Figure 1). The heart-to-mediastinum count ratios (H/M Ratios) were calculated from the mean counts per pixel in the ROIs over the heart and mediastinum before and after TEW correction.

Statistical Analyses

All the H/M ratios in the clinical study were expressed as Mean \pm SD and were analyzed with Student's t test. Statistical significance was defined as $P < 0.05$. The receiver operating characteristic (ROC) curve analysis was employed to evaluate the accuracy of differentiating PD patients from non-PD patients.

Results

Figure 2 shows the counts per pixel in the heart and mediastinal ROIs and the H/M ratios with and without scatter correction in the phantom study. In the phantom simulating normal function, the estimated H/M ratio

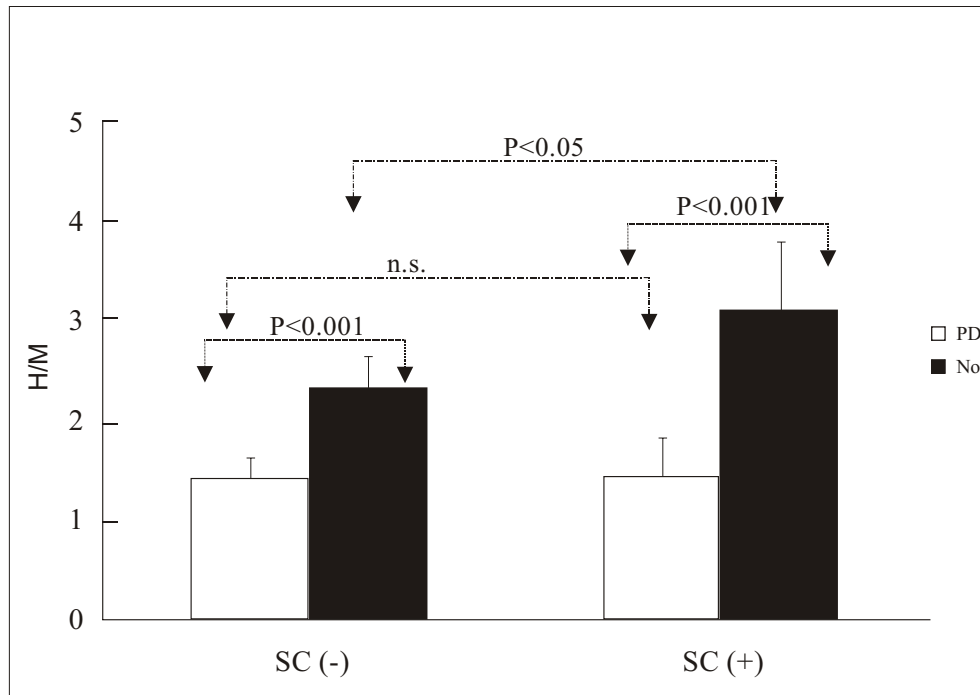


Figure 3. Comparison of H/M ratios (Mean \pm SD) in patients with Parkinsonism in images processed with and without scatter correction. SC (-): without scatter correction; SC(+): With scatter correction; PD: Parkinson's Disease group; No: non-PD group

Group	Diagnosis	Number of cases
PD Group	Parkinson's Disease	21
	Dementia of Lewy Body	20
Non-PD Group	Multiple System Atrophy	34
	Dentatorubral-pallidoluysian Atrophy	1
	Cortico-basal Degeneration	01
	Amyotrophic Lateral Sclerosis	02
	Alzheimer's Disease and Dementia	03
	Pure Akinesia	01
	Chronic Inflammatory Demyelinating	01
	Polyradiculoneuropathy	
	Cerebrovascular Disease & Others	07
	Psychological Problems	02

Table 1. Patient population

	Near H/M	Far H/M	In between near and far
Normal Uptake			
SC(-)	1.94	1.91	1.02
SC(+)	2.39	2.33	1.03
No uptake			
SC(-)	1.44	1.35	1.07
SC(+)	1.24	1.25	0.99

Near H/M: H/M calculated keeping the distance between heart to liver ver near

Far H/M: H/M calculated keeping the distance between heart to liver far

SC(-): Without scatter correction

SC(+): With scatter correction

Table 2. Influence of Heart-to-Liver Distance on H/M Ratio

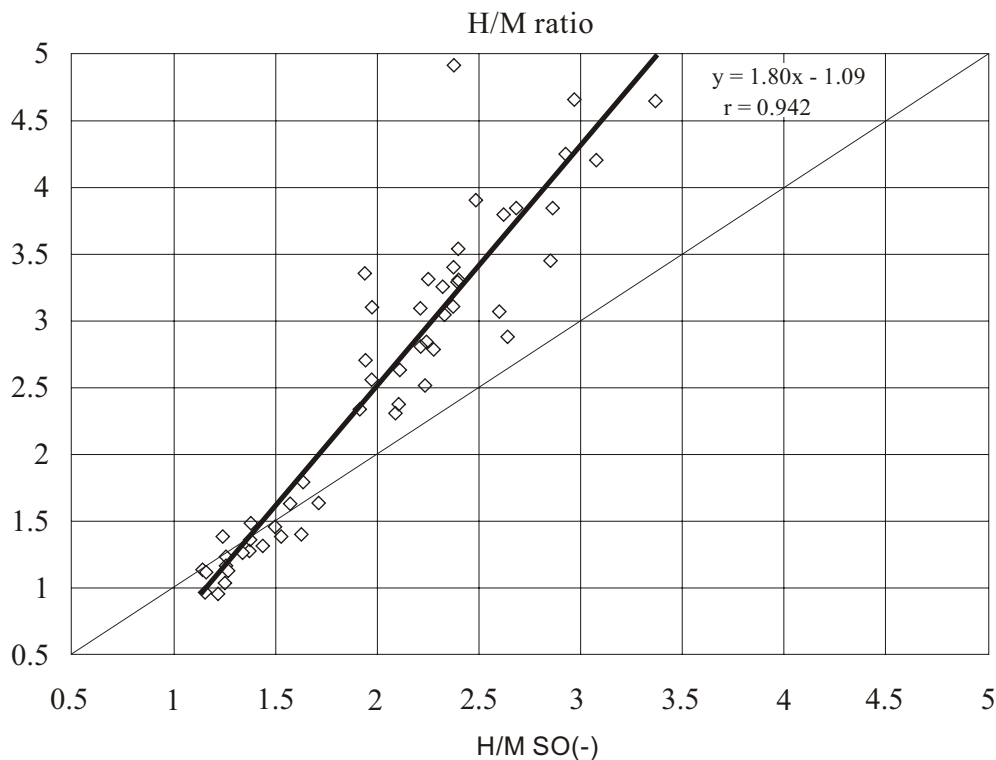


Figure 4. Relationship between H/M ratios with and without scatter correction. SC(-): without scatter correction; SC(+): With scatter correction; H/M SC(-): H/M ratio obtained without scatter correction; H/M SC(+): H/M ratio obtained with scatter correction.

increased after scatter correction. This is due to the more marked count reduction in the mediastinum compared to that in the heart. In contrast, in the phantom with no cardiac uptake, scatter correction produced a decreased H/M ratio by reducing the heart count much more than the mediastinal counts.

The influence of hepatic radioactivity on the H/M ratio was assessed by changing the distance between the heart and liver. The H/M ratio remained stable independent of the heart-to-liver distance in the phantom simulating normal function (Table 2); this stability was observed in the H/M values obtained from images with and without scatter correction. On the other hand, in the phantom simulating no cardiac output, the H/M ratio changed depending on the distance when not performing scatter correction and kept unchanged in the scatter corrected images, indicating that scatter correction could circumvent the distance-dependent variation of the H/M ratio.

Clinical Study

Figure 3 depicts the H/M ratios in PD and non-PD groups with and without scatter correction. Statistically significant difference was observed between the two groups both in scatter-corrected and uncorrected images. The H/M ratios showed no appreciable change after scatter correction in the PD group, while scatter correction yielded significantly increased H/M ratios in the non-PD group. Hence the differences were widened following scatter correction between the PD and non-PD groups.

Figure 4 illustrates the effect of scatter correction in each

patient and relationship between H/M ratios with and without scatter correction. Increased H/M ratios after scatter correction were observed in patients with relatively well preserved MIBG uptake, whereas scatter correction resulted in decreased or unaltered H/M ratios in cases where the values were 1.5 or less.

The results of ROC analysis in separating PD and DLB from others are illustrated in figure 5. The areas under the curves were 0.961 and 0.941 in the diagnosis using uncorrected and scatter corrected H/M values, respectively. They were found to be statistically insignificant.

Discussion

Quantitative evaluation with the target-to-background count ratio is frequently used in routine scintigraphic studies because of its practicability. However, its accuracy is often degraded by scattered photons (15). With regard to the H/M ratio in I-123 MIBG imaging, scattered photons originating from the lungs contribute significantly to the mediastinal counts. In addition low cardiac uptake of MIBG may augment the influence of scattered photons from the liver to the heart ROI. Furthermore, the H/M ratio varies depending on the collimator selected and the variation is more remarkable when using low energy (LE) as compared with medium-energy (ME) collimators (10,11). The planar H/M ratios are less influenced by the septal penetration and scattered photons from liver activity when using medium-energy collimator (10). However, the

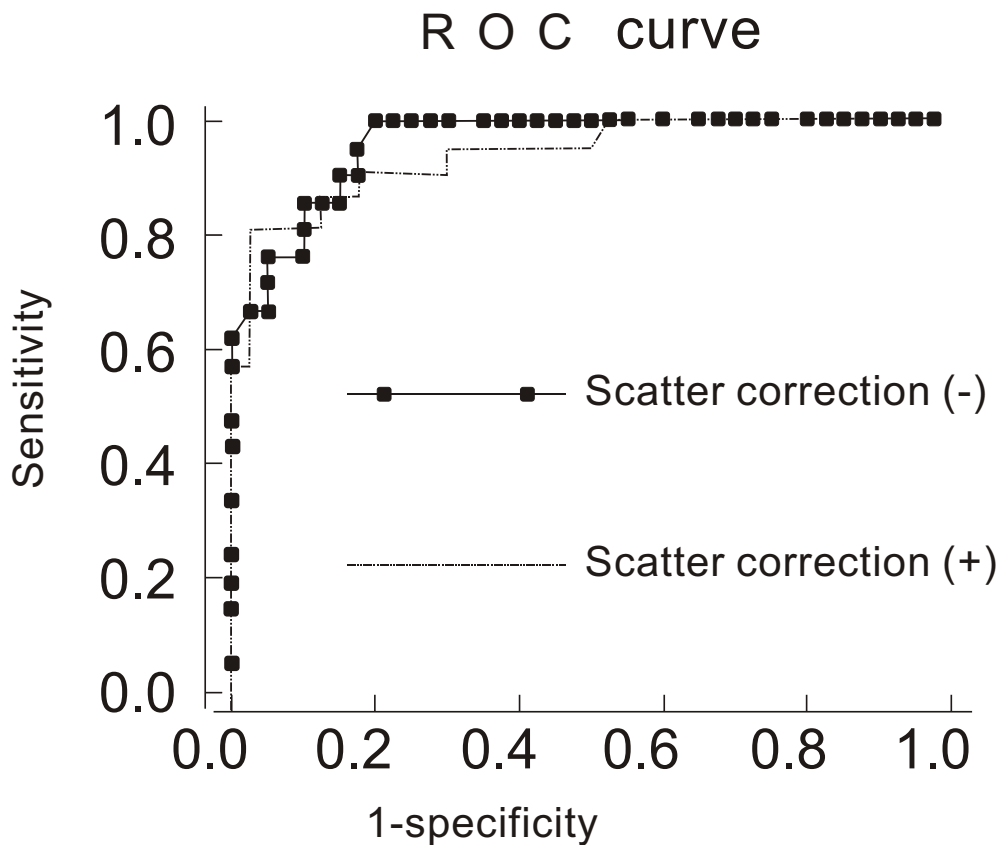


Figure 5. Accuracy of diagnosing Parkinson's disease using H/M ratios with and without scatter correction. Scatter correction (-): Without scatter correction; Scatter correction (+): With scatter correction.

low-energy collimator is still widely used in radionuclide imaging. Keeping in view the above practice, in the present study we implemented phantom as well as clinical imaging using the low-energy collimator under different grades of cardiac MIBG uptake in order to estimate the effect of scatter correction on quantification.

The results of the phantom experiment clarified the inherent inaccuracy of the H/M ratio. The H/M value was underestimated in the phantom simulating normal cardiac uptake and overestimated in the condition of severely decreased uptake. One of the reasons causing this error in estimation is photon scattering that could be overcome in clinical planar imaging.

The scatter fraction varies widely depending on the level of radioactivity in the target organ and adjacent tissues, and their anatomical relationship. In the condition of normal cardiac uptake, the scatter fraction in the heart ROI is smaller than that in the mediastinal ROI because the high cardiac count dominates scattered photons from adjacent organs resulting in an increase in the H/M value after scatter correction. In contrast, when cardiac uptake is severely reduced, the scatter fraction in the heart ROI is higher than that in the mediastinal ROI. This is due to the close proximity of liver to the heart ROI. In this case, the liver acts as the major source of scattered photons. Scatter correction decreases the H/M ratio in this condition. Hence, scatter correction may work to reduce the overlap of the H/M ratios

among subjects with narrow differences of cardiac uptake. Moreover, scatter correction offers stable measurement of the H/M ratio regardless of the heart-to-liver distance by reducing the distance dependent effect of photon scattering (Table 2). This result demonstrates the usefulness of scatter correction in clinical practice in circumventing the inter-individual variations resulting from the difference of anatomical relationship between heart and liver.

A number of authors have reported the reduction of MIBG cardiac uptake in PD patients and not in non-PD patients (2,3,6). Meanwhile, the decrease of cardiac MIBG uptake in non-PD patients has also been reported, leading to overlap in H/M ratios obtained in PD and non-PD patients (8). None of the above articles employed scatter correction in calculating the H/M ratios. In the current study, scatter correction increased the H/M values in subjects with well-preserved cardiac sympathetic nerve function, while not in patients with severely impaired function (Figure 4). However ROC analysis revealed that scatter correction did not improve the diagnostic power (Figure 5). There are two possible reasons accounting for this result; number one reason being, that MIBG examination has inherently high diagnostic power regardless of the insufficient accuracy of the H/M index without scatter correction. This explanation is supported by the fact that the majority of papers in literature have reported acceptable diagnostic accuracy in differentiating PD from non-PD even without employing

scatter correction technique. The second reason could be that there are only a limited number of mild PD cases whose H/M values are in the border zone between PD and non-PD. There is a need for further studies including certain number of mild PD cases to clarify this aspect. Nevertheless on the basis of the present study and of several studies reported in literature it has been proven that conventional MIBG imaging can distinguish most of the patients with neurological disorders into PD and non-PD groups even without employing scatter correction.

Conclusions

Scatter correction was applied to MIBG planar images for calculating H/M ratios, and verified its feasibility through phantom and clinical studies. Scatter correction improved the separation of preserved cardiac uptake from reduced uptake, and stabilized the H/M calculations by reducing the influence of scatter photons from other adjacent organs. In differentiating patients with Parkinsonism, scatter correction did not offer any significant incremental diagnostic value to conventional images without scatter correction. Nevertheless the scatter correction method deserves consideration for use in calculating H/M ratio, because of its simplicity and effectiveness in eliminating the possible inaccuracies of the H/M ratio resulting from variations in the heart to liver distance.

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